REMARKS

The Office Action dated July 29, 2003, has been received and reviewed. Claims 1-32 are pending in the present application. Claims 33-73 have been withdrawn from consideration. Claims 1-32 stand rejected. Applicants respectfully request reconsideration of the application in view of the amendments to the claims and the arguments below.

Applicants note that they have amended the abstract of the application to more clearly define that which is clearly indicative of the invention to which the claims are directed. Applicants have also amended the title of the invention to be indicative of the invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objections to the abstract and title.

I. Claim Amendments

Claims 1, 4-9, 11-14, 16, 18, and 22-32 have been amended to better state that which is the invention and to correct minor informalities. Claims 2-3 have been cancelled. Claims 33-72 have been withdrawn from consideration. Support for these amendments can be found throughout the specification, examples and figures of the present application.

II. Claim Objections

Claims 4, 8, 11-13, 18 and 22-32 stand objected to as the Office Action indicated that the article before "DNA" in Claims 4, 18 and 29 should be deleted. Applicants have deleted the article before "DNA". Accordingly, Applicants respectfully request that the objections to Claims 4, 8, 11-13, 18 and 22-32 be withdrawn.

Claims 8, 11, 12-13 and 24-25 stand objected to for minor informalities. Applicants have corrected these informalities as suggested by the Examiner. Accordingly, Applicants respectfully request that the objections to Claims 8, 11, 12-13 and 24-25 be withdrawn.

Claims 22-23 and 25-32 stand objected to for having an improper article. Applicants have amended the claims to start with a proper article. Accordingly,

Applicants respectfully request that the objections to Claims 22-23 and 25-32 be withdrawn.

III. Rejections under 35 U.S.C. § 112, first paragraph

A. Enablement

Claims 1-32 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, to make and/or use the invention commensurate with the scope of the claims. Applicants respectfully traverse this rejection.

The Office Action alleges that Claims 1, 14 and 25 do not provide enablement for 20-455 nucleotide fragments of SEQ ID NO: 1 or nucleic acids that hybridize to SEQ ID NO: 1 and that are "responsive to" a *Nic* gene product. Applicants have amended Claim 1 to recite an active fragment of at least 200 consecutive nucleotides and Claims 14 and 25 to recite that the fragment comprises 20 to 455 consecutive nucleotides of SEQ ID NO: 1. Applicants note that the specification recites on page 10, line 31 to page 11, line 8, that "the present invention is, in one preferred embodiment, based upon an isolated nucleic acid (e.g., SEQ ID NO: 1 or a fragment thereof consisting of, desirably, at least 20-450 consecutive nucleotides, preferably, at least 30-400 consecutive nucleotides, more preferably, 50-350 consecutive nucleotides, and, most preferably, 100-300 or 200-400 consecutive nucleotides) that is or contains at least one *cis*-acting regulatory element, which exists upstream of the plant quinolate phosphoribosyl transferase (QPTase) and putrescence methyl transferase (PMTase) coding sequences. Another example is the *Nic* gene product responsive element obtained from the sequence disclosed in U.S. Patent No. 5,459,252, herein expressly incorporated by reference in its entirety." Applicants point out that the specification in numerous other instances provides fragments from 20 to 455 nucleic acids. *See*, page 4, line 13, and page 17, line 20.

Furthermore, the Applicants note that the recitation "responsive to a *Nic* gene product" may be found throughout the application, particularly on page 4, line 17. It is further noted that the phrase "responsive to a *Nic* gene product" is for example, an "increase or decrease transcription of an operatively associated gene and hence increase or decrease the level of the encoded protein of interest in the host cells". *See,* page 4, lines 17-19. Accordingly, Applicants submit that the recitation "responsive to a *Nic* gene product" in part (b), now part (c), is clear with respect to Claims 14 and 25.

Furthermore, Applicants note that one approach for reducing the level of a biological product, such as nicotine, is to reduce the amount of a required enzyme (i.e. QPTase and PMTase) in the biosynthetic pathway leading to that product. Where the affected enzyme naturally occurs in a rate-limiting amount (relative to the other enzymes required in the pathway), any reduction in that enzyme's abundance will decrease the production of the end product. If the amount of the enzyme is not normally rate-limiting, its presence in a cell can be reduced to rate-limiting levels in order to diminish the pathway's output. Applicants further note that the examples assessed GUS activity and that they have amended the claims to recite an active fragment. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112 rejections.

Additionally, the Office Action alleges that the specification fails to provide guidance for exact hybridization or amplification conditions. Applicants respectfully disagree with this assertion. Applicants note that the specification teaches for example, "hybridization of such sequences may be carried out under conditions of reduced stringency or even stringent conditions (e.g., conditions represented by a wash stringency of 0.3 M NaCl, 0.03 M sodium citrate, 0.1% SDS at 60°C or even 70°C to DNA with the sequence given herein as SEQ ID NO: 1 using a standard *in situ* hybridization assay. *See* J. Sambrook et al., Molecular Cloning, A Laboratory Manual (2d Ed. 1989)(Cold Spring Harbor Laboratory)). In general, such sequences will be at least 65% similar, 75% similar, 80% similar, 85% similar, 90% similar, or even 95% similar, or more, with the sequence given herein as SEQ ID NO: 1. Determinations of sequence similarity are made with the two sequences aligned for maximum matching; gaps in either of the two sequences being matched are allowed in

maximizing matching. Gap lengths of 10 or less are preferred, gap lengths of 5 or less are more preferred, and gap lengths of 2 or less still more preferred." *See,* page 17, line 32 to page 18, line 12. Thus, one of skill in the art could readily follow these procedures. However, to speed prosecution of the instant application, Applicants note that they have amended the claims to recite that the isolated nucleic acid hybridizes under stringent conditions. Additionally, Applicants note that they have amended the claims to note the 95% sequence similarity. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1-32.

Applicants further note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Furthermore, the test for whether or not the enablement requirement has been met involves determining whether or not practice of the invention as claimed involves "undue experimentation". It has long been settled that "the key word is 'undue', not 'experimentation'". *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976).

For the presently claimed application, Applicants submit that the application of the current technology requires routine effort, and not undue experimentation. Applicants note that suppression has been used as a tool to identify gene function and that as such, a wide range of application from targets for therapeutics or pesticides and even therapy. *See,* Sharma et al., *Anticancer Res.* 1996 16(1) 61-9); Mann et al, *J. Clin Invest*, 2000 106(9) 1071-5. It has been demonstrated that in some plants and organisms, the production of double-stranded RNA provides a more efficient method of post-transcriptional suppression and that in the case of transgenic plants, a high percentage of transgenic lines have shown significant reduction of the target gene product and a reduced amount of activity. *See,* Waterhouse et al., 1998, *PNAS*, 95:13959-13964.

The molecular decoy approach of the present application has several advantages over the suppression approach including the fact that it is easier to reproduce. With the approach claimed in Independent Claims 11 and 24, one of skill in the art could readily use the approach claimed because it requires only that a

binding site be identified in the regulatory region of one regulated gene. Both U.S. Patent No. 6,060,310 and U.S. Patent No. 6,262,033 illustrate the regulation of gene expression by introduction of decoys for particular transcription factors. Accordingly, Applicants submit that one of skill in the art could readily practice the invention as presently claimed in the application.

The Office Action expresses concern that Applicants have not demonstrated actual reduction to practice of particular embodiments of the invention. Applicants note that disclosure in the specification of an actual reduction to practice is *not* necessary to satisfy the enablement requirement (*see*, MPEP §2164.02; *Gould v. Quigg*, 822 F.2d 1074, 1078; 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)). Accordingly, Applicants submit that there is sufficient guidance to direct a person of skill in the art to use the isolated nucleic acid or an active fragment thereof as claimed. Applicants submit that one of skill in the art could readily formulate the isolated nucleic acid or fragment claimed. Moreover, the Court of Appeals for the Federal Circuit has held that it is not necessary for the specification or claims to list all operative embodiments, or to exclude all inoperative embodiments, stating: "Even if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude ... possible inoperative substances...'". *Atlas Powder Co. v. DuPont*, 750 F.2d 1569; 224 USPQ 409 (CAFC 1984). All that is required by § 112 is that one skilled in the art may determine the inoperative embodiments with no more than routine skill. Applicants submit that this standard is satisfied in the present application. The Examples note that GUS activity was assessed by dividing plants into roots, stems, and leaves and that each plant tissue was transformed with a different *NtQPT1* truncation construct. Accordingly, Applicants submit that the present application is enabled. Thus, one of skill in the art would readily be able to follow the invention as presently claimed.

The Office Action also questions which of the fragments reduce the level of nicotine in a plant and do so without negatively affecting other functions in the plant. The examples presented in the application illustrate in Example 1 that the *NtQPT1* *cis*-acting element is located between –586 and –2000 bp 5' of the transcription start site, and in Example 2 that binding of *Nic* gene products is located between

approximately –1000 and -600 or -700 bp of the *NtQPT1* promoter as determined by GUS activity in *Nic*$^{+}$*/nic*$^{-}$ and *nic*$^{-}$*/nic*$^{-}$ plants. As noted in the *Manuel of Patent Examining Procedure* (M.P.E.P.), "[c]ompliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed." M.P.E.P. § 2164.02. Moreover, M.P.E.P. § 2164.02 further states that "because only an enabling disclosure is required, applicant need not describe all actual embodiments." Thus, Applicants submit that the present application provides enablement for a method of making a transgenic tobacco plant having a reduced amount of nicotine, comprising introducing a nucleic acid consisting essentially of a *Nic* gene product responsive element into at least one tobacco plant cell so as to produce at least one transformed tobacco plant cell, wherein said at least one transformed tobacco plant cell comprises said nucleic acid in a copy number sufficient to reduce the amount of nicotine in a tobacco plant regenerated from said cell as compared to the amount of nicotine that would be present in the absence of said nucleic acid; and regenerating said at least one transformed tobacco plant cell so as to obtain said tobacco plant. One of skill in the art would be able to routinely ascertain which pieces of the given sequence have competitive inhibition so as to not activate QPTase. Thus, the observed effects provide one of ordinary skill in the art the tools to conduct routine experimentation to devise a protocol as provided by the present application. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that the applicant was in possession of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1 and 4-32.

B. Written Description

Claims 1-32 are also rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors

at the time the application was filed had possession of the claimed invention. Applicants respectfully disagree with this assertion.

Applicants note that the U.S.P.T.O. has clarified the standard for examining applications for compliance with respect to the written description requirement of 35 U.S.C. §112, first paragraph. These guidelines state, in part:

> The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed . . .. Consequently, rejection of an original claim for lack of written description should be rare.

(Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1105 (Jan. 5, 2001); emphasis added).

Applicants respectfully contend that the specification does provide a sufficient written description so that one skilled in the art would appreciate that the Applicants were in possession of the claimed invention at the time of filing. Adequate written support does not require that the application contain an exhaustive enumeration of all possible peptide fragments. Applicants submit that a person of skill in the art can readily envision fragments comprising the amino acid sequence of SEQ ID NO. 1 or active fragments of the present application. Applicants note that "an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1105. Along these lines, one of skill in the art could readily search the United States Patent Office's nucleotide database to determine the region of the promoter. A quick search of the patent cited in the Office Action illustrates that the sequence is found in U.S. Patent 5,837,876 in the 2010 base pair sequence (SEQ ID NO:1) of the 5' region of TobRD2, and that it may be found in the Δ1.4 promoter (SEQ ID NO:3) with GUS; Δ1.3 promoter (SEQ ID NO:4) with GUS;

and the Δ1.0 promoter (SEQ ID NO:5) with GUS. This illustrate that the applicants were in possession of the genus claimed at the time this application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph to Claims 1-32.

IV. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-32 stand rejected under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph rejections in view of the claim amendments and the following remarks.

The Office Action alleges that Claims 1, 14 and 25 are indefinite in their recitation of "acids". Applicants have amended Claims 1, 14 and 25 to recite either "the isolated nucleic acid" or "an isolated nucleic acid". Applicants submit that this amendment clarifies Claims 1, 14 and 25. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1, 14 and 25.

The Office Action also alleges that Claims 1, 14 and 25 are indefinite in their recitation of "responsive to a *Nic* gene product" in part (b), now part (c). Applicants note that the recitation "responsive to a *Nic* gene product" may be found on page 4, line 17. It is further noted that the phrase "responsive to a *Nic* gene product" is for example, an "increase or decrease transcription of an operatively associated gene and hence increase or decrease the level of the encoded protein of interest in the host cells". *See,* page 4, lines 17-19. Applicants have removed this language from Claim 1. Accordingly, Applicants submit that the recitation "responsive to a *Nic* gene product" in part (b), now part (c), is clear with respect to Claims 1, 14 and 25.

The Office Action also alleges that Claims 1, 14 and 25 are indefinite in their recitation of "wherein said fragment is between 20-455 consecutive nucleotides". Applicants have amended Claim 1 to remove this recitation thus mooting this rejection for this claim. Applicants believe that Claims 14 and 25 are clear in their recitations that this is the length of the fragment. However, in an effort to expedite prosecution of this application, Claims 14 and 25 have been amended to recite that the

fragment comprises 20 to 455 consecutive nucleotides of SEQ ID NO: 1. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1, 14 and 25.

Claims 5, 7, 9, 16-17 and 27-28 stand rejected as allegedly being indefinite as being unclear "if the nucleic acid is part of the recombinant nucleic acid construct". Applicants have amended Claims 5, 7, 9, 16 and 27 to recite a recombinant nucleic acid construct. Claims 17 and 28 depend from Claims 16 and 27 and are therefore now in condition for allowance for the same reasons. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 5, 7, 9, 16-17 and 27-28.

Claim 8 has been amended as suggested by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claim 8.

Claim 12 has been amended to recite "tobacco" before the first instance of "leaves" in line 2. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claim 12.

Claim 13 stands rejected as allegedly the term "regenerated" is unclear. Applicants respectfully disagree with this assertion, but in an effort to expedite prosecution of the present application, Applicants have amended Claim 13 to recite "reproduced" rather than regenerated. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claim 13.

Claim 16 stands rejected for lacking antecedent basis for the term "isolated". Applicants have amended Claim 16 to remove this term. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claim 16.

Claims 23 and 32 stand rejected as allegedly being indefinite as it is "not clear if the tobacco seed comprises the *Nic* responsive element. Applicants have amended Claims 23 and 32 to recite that the seed comprises the *Nic* responsive element. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 23 and 32.

Claims 24, 27 and 29 are rejected as purportedly being indefinite for its recitation of "exogenous". The Office Action alleges that it is not clear how the

nucleic acids could be exogenous to the tobacco plant. Applicants note that Claim 24, of which claims 27 and 29 depend from, recites that the "exogenous nucleic acid consists essentially of a *Nic* gene product responsive element". Applicants note that an exogenous nucleic acid construct comprising a *Nic* gene product responsive element may be introduced into a tobacco plant cell to produce a transformed tobacco plant cell. Thus, these nucleic acids may be exogenous to the tobacco plant. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 24, 27 and 29.

V. Rejections under 35 U.S.C. § 102(b)

Claims 1-10 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Conkling et al., WO 97/05261. Applicants respectfully traverse this rejection for the reasons set forth below.

Case law holds and the M.P.E.P. states that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Additionally, anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention. *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000). WO 97/05261 fails to disclose the subject matter contained in Claims 1-10.

Applicants note that amended Claim 1, of which claims 2-10 depend from, recites, "An isolated nucleic acid selected from the group consisting of: (a) the isolated nucleic acid sequence of SEQ ID NO: 1 or an active fragment thereof, wherein said fragment is at least 200 consecutive nucleotides; and (b) a nucleic acid sequence which is at least 95% identical to the nucleic acid sequence of (a)." Support for the amendments for the identity language may be found on page 18, lines 5-8. Additionally, support for fragments may be found throughout the specification, particularly on page 11, line 3. Applicants submit that WO 97/05261 fails to disclose

such an isolated nucleic acid. Therefore, WO 97/05261 fails to anticipate Claims 1 and 4-10 of the present application. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 102(b) rejections to Claims 1 and 4-10.

VI. Double Patenting

Claims 1-10 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 16-22 of U.S. Patent No. 5,837,876. Applicants respectfully disagree with this assertion. Applicants note that with respect to the double patenting rejections based on 35 U.S.C. § 101, M.P.E.P. § 804 provides:

Applicants note that the sequence claimed in Claim 1 of the present application is not the same as SEQ ID NO. 1 of U.S. Patent No. 5,837,876. Furthermore, the pending claims are not obvious in view of the claims of U.S. Patent No. 5,837,876. Accordingly, Applicants submit that Claims 1 and 4-10 are patentably distinct from U.S. Patent No. 5,837,876, thus mooting this rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of the nonstatutory double patenting rejection.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,

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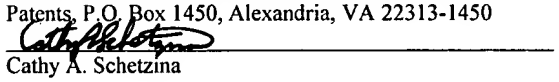

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